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(21) International Application Number: PCT/US85/02375 (22) International Filing Date: 3 December 1985 (03.12.85) (31) Priority Application Number: 678,641 (32) Priority Date: 6 December 1984 (06.12.84) (33) Priority Country: US (71) Applicant: RENAL SYSTEMS, INC. [US/US]; 14905 28th Avenue North, Minneapolis, MN 55441 (US). (72) Inventors: COSENTINO, Louis, C. ; 2435 Holly Lane North, Plymouth, MN 55447 (US). HNOJEWYJ, Anatol, M. ; 822 University Avenue, N.E., Minneapolis, MN 55413 (US). JANSEN, Walter, B. ; 4015 Evergreen Lane, Plymouth, MN 55441 (US).		(74) Agent: VIDAS, Scott, Q.; Vidas & Arrett, P.A., 2925 Multifoods Tower, 33 South Sixth Street, Minneapolis, MN 55402 (US). (81) Designated States: AT, AT (European patent), AU, BE (European patent), CH, CH (European patent), DE, DE (European patent), DK, FI, FR (European patent), GB, GB (European patent), IT (European patent), JP, LU, LU (European patent), NL, NL (European patent), NO, SE, SE (European patent). Published <i>With international search report.</i> <i>With amended claims.</i>
(54) Title: BACTERIOSTATIC HEMODIALYSIS CONCENTRATE (57) Abstract Hemodialysis bicarbonate and acid concentrates which are bacteriostatic and bactericidal. Sodium bicarbonate concentrate is made biocidal by including greater than 28 grams per liter of sodium chloride. The excess sodium chloride in the bicarbonate concentrate is obtained from a decrease in the sodium chloride concentration in the acid concentrate. Powdered mixtures having the proper ratios of sodium chloride to bicarbonate may be dissolved in purified water used in hemodialysis to obtain the biocidal hemodialysis concentrates.		

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BACTERIOSTATIC HEMODIALYSIS CONCENTRATEI. DESCRIPTIONField of the Invention

This invention is directed to hemodialysis solutions and more particularly to dialysis concentrate.

Background of the Invention

Dialysis fluids for hemodialysis must contain either acetate, bicarbonate or other similar buffers to maintain the pH of the solution within acceptable limits.

Most hemodialysis solutions contain either sodium acetate or sodium bicarbonate buffer.

Bicarbonate hemodialysis is preferred over acetate hemodialysis. Less dialysis induced morbidity and vascular instability has been reported when bicarbonate is used instead of acetate. When acetate is metabolized by the body undesirable triglyceride levels may be formed.

Most dialyzing solutions are prepared by use of commercial liquid concentrate. When appropriately diluted, the desired electrolyte concentration is obtained. Sodium acetate has been traditionally used rather than bicarbonate to maintain stability in storage. Acetate concentrate was usually considered to be bactericidal.

The major reason bicarbonates are less desirable than acetate is the lack of ionic stability and the growth of microorganisms within the bicarbonate concentrate. Traditionally, sodium bicarbonate concentrate includes sodium chloride. However, the level of sodium chloride in the concentrate has always been less than about 23.8 grams per liter.

Such solutions are not adequately bactericidal or bacteriostatic.

Summary of the Invention

The present invention provides compositions which, when properly diluted, yield bicarbonate hemodialysis solution. The inventive compositions provide acid hemodialysis

concentrate and bicarbonate concentrate which are bacteriostatic and bactericidal in the same manner as acetate concentrate.

Hemodialysis solution is typically prepared by
5 mixing together and diluting an acid concentrate and a bicarbonate concentrate. The typical acid concentrate includes sodium chloride, calcium chloride, potassium chloride, magnesium chloride, acetic acid and dextrose. The sodium chloride level in the acid concentrate was typi-
10 cally at a concentration which resulted in a pH of between 0.8 and 3.0 which is bacteriostatic. As stated above, bicarbonate concentrate was prepared with sodium bicarbonate and sodium chloride concentration below 23.8 grams per liter. Such prior art bicarbonate concentrates are not
15 bacteriostatic or bactericidal.

The inventor has discovered that a bactericidal and bacteriostatic bicarbonate concentrate is formed whenever the sodium chloride concentration exceeds approximately about 28 grams per liter. In order to add additional
20 sodium chloride to a bicarbonate concentrate, the inventor reduced the quantity of sodium chloride in the acid concentrate such that the total amount of sodium chloride present in the final hemodialysis solution would be unchanged. Surprisingly, the inventor found that when the bicarbonate
25 concentrate is made bactericidal by increasing the sodium chloride concentration, the corresponding decrease of sodium chloride in the acid concentrate did not make the acid concentrate non-bacteriostatic. It was found that the pH of acid concentrate having a lower sodium chloride content was between 0.8 and 3.0 which provides bacteriostatic
30 properties.

Bacteriostatic and bactericidal qualities of the acid concentrate and bicarbonate concentrate solutions are achieved with the use of materials which are already in
35 routine application in dialysis therapy. Long term studies

to show compatibility for human use is not required since the final hemodialysis solution will have the same parameters as was previously provided by the prior art mixtures. The distinct advantages in using bicarbonate may be
5 achieved without the undesirable microorganism growth which had previously been encountered with the use of bicarbonate concentrate.

Hemodialysis solutions may be formulated on site with the use of three stream artificial kidney machines
10 such as the AK-10 system as sold by Gambro, Inc. The advantages of the invention may be realized by shipping powdered chemical compositions which are pre-measured such that the addition of a specified quantity of water will result in the bacteriostatic and bactericidal concentrates.
15 The powdered chemicals may be diluted with water through the use of a Renapak™ processing machine as sold by Renal Systems, Inc of Minneapolis, Minnesota. Alternatively, the acid concentrate may be prediluted with water to its bacteriostatic concentration. Either the powdered bicarbonate
20 concentrate composition or the diluted bicarbonate concentrate composition may then be utilized. In any of the forms which the hemodialysis solution user receives the composition, the compositions will be bactericidal and bacteriostatic. Powdered formulations are of course bac-
25 teriostatic to begin with and when properly diluted provide the bacteriostatic concentrate properties of the invention.

Detailed Description of the Invention

Bicarbonate containing hemodialysis solution
30 usually includes sodium chloride, calcium chloride, potassium chloride, magnesium chloride, acetic acid, sodium bicarbonate and, optionally, dextrose. The exact quantity of each ion within a hemodialysis solution may vary depending on the needs of a particular patient.
35 However, typical hemodialysis solution has about 140

milliequivalents per liter of sodium, 3.5 milli quivalants per liter of calcium, 1 milliequivalent per liter of magnesium, 1 milliequivalants per liter of potassium, 106.5 milliequivalents per liter of chloride, 35 milliequivalents per liter of bicarbonate and 4 milliequivalents per liter of sodium acetate. The concentration of each may be vary up or down in custom prepared solutions. Most manufacturers supply a series of hemodialysis solutions which have varying concentrations of the chemical species there-
10 within.

The advantages of the invention may be achieved such that any of the commercially available, standard hemodialysis solutions or custom hemodialysis solutions may be produced.

15 The invention involves providing sufficient sodium chloride in a bicarbonate concentrate such that the concentration of sodium chloride in the bicarbonate concentrate is at least 28 grams per liter. The higher the concentration of sodium chloride in the bicarbonate concentrate, the lower the sodium chloride concentration is in the acid concentrate. The total amount of sodium chloride in hemodialysis solution prepared from the bactericidal and bacteriostatic bicarbonate and acid concentrates remains unchanged. As the quantity of sodium
20 chloride within the bicarbonate concentrate increases it decreases in the acid concentrate, such that the total amount of sodium chloride in the final hemodialysis solution is unchanged.

It has been found that a bicarbonate concentrate
30 of 28.0 grams NaCl per liter will be bacteriostatic. However, since such a solution is at the lower limit which will create a bacteriostatic solution, the concentrate should be aged for seven days and tested for growth before use. The concentrate is bacteriostatic after aging for about one
35 w ek. There is a possibility of bacterial growth before

-5-

the seven days have elapsed at the marginally bacteriostatic concentration.

Preferably, the concentration of NaCl is grams per liter in the bicarbonate concentrate is about 35.3 or higher. The higher concentrations of salt have even greater bacteriostatic properties. The concentration of NaCl is limited by its solubility characteristics when in solution with sodium bicarbonate. At temperature ranges in which the concentrate will probably be used in forming dialysis solution the maximum concentration of NaCl would be about 200 grams/liter.

The normal concentration of bicarbonate in a human body is about 20 milliequivalents (meq.) per liter. Hemodialysis usually involves a solution having about 39 meq. bicarbonate per liter. However, in some applications, the dialysis may involve 20 to as low as 15 meq. bicarbonate per liter. The maximum sodium bicarbonate in the bicarbonate concentrate would be about 164 grams/liter if the concentrate is prepared at an elevated temperature.

The concentration of sodium chloride in the acid concentrate depends on the concentration of sodium chloride in the bicarbonate concentrate. The maximum sodium chloride concentration in the acid concentrate is limited by the necessity of maintaining at least 28 grams per liter of sodium chloride in the bicarbonate concentrate. The concentration of sodium chloride in the acid concentrate may be zero, with all of the sodium chloride being present in the bicarbonate concentrate.

Example 1

30	(A) <u>Acid Concentrate</u>	<u>Grams per Liter</u>
	Sodium Chloride	118.4
	Calcium Chloride	9.5
	Potassium Chloride	5.5
	Magnesium Chloride	3.7
35	Acetic Acid	8.8
	Dextrose	73.7

(B)	<u>Bicarbonate Concentrate</u>	<u>Grams per Liter</u>
	Sodium Chloride	52.9
	Sodium Bicarbonate	66.0

In order to make up 36.83 liters of prepared hemodialysis solution, acid concentrate and bicarbonate concentrate were prepared to the above concentrations. The bicarbonate concentrate consisted of 96.8 grams NaCl and 120.6 grams of sodium bicarbonate diluted to 1.83 liters with water.

The acid concentrate was prepared by adding 118.4 grams NaCl, 9.5 grams calcium chloride, 5.5 grams potassium chloride, 3.7 grams magnesium chloride, 8.8 grams acetic acid and 73.7 grams dextrose to water to a total of 1.0 liter.

Both the acid concentrate and bicarbonate concentrate prepared as detailed above are bacteriostatic. Dialysis solution is prepared by adding 34.83 liters of water, 1.83 liters of bicarbonate concentrate and 1.0 liters of acid concentrate together.

The bicarbonate and/or acid concentrates may be prepared from the raw powder constitutes singly or more preferably from prepackaged containers which, when diluted as indicated on the label, will yield the bacteriostatic concentrates of the invention.

In considering this invention it should be remembered that the present disclosure is illustrative only, and that the scope of the invention is determined by the appended claims.

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WHAT IS CLAIMED IS:

1. Bacteriostatic animal dialysis concentrate comprising:
sodium bicarbonate and sodium chloride in water, said sodium chloride having a concentration greater than 23.8 grams per liter.
2. A composition for use in preparing animal dialysis solution from an acid concentrate and a bicarbonate concentrate, said bicarbonate concentrate comprising:
 - a) sodium bicarbonate;
 - b) sodium chloride;
 - c) water; and
 - d) the concentration of said sodium chloride being at least 28 grams per liter of water and no greater than 200 grams per liter.
3. A composition of matter adapted for use as a hemodialysis bicarbonate concentrate comprising: sodium chloride and sodium bicarbonate, said sodium chloride being in a quantity sufficient such that upon dilution with water said hemodialysis bicarbonate concentrate is bacteriostatic.
4. A composition comprising sodium chloride and sodium bicarbonate for use in preparing dialysis bicarbonate concentrate solution, said sodium chloride being in a ratio to said sodium bicarbonate such that upon dilution to obtain a bicarbonate concentrate having the desired bicarbonate concentration, said sodium chloride has a concentration greater than 28 grams per liter.
5. A composition for use in preparing dialysis bicarbonate concentrate, wherein the desired concentration



of sodium bicarbonate in the dialysis bicarbonate concentrate is X grams per liter, the composition comprising: sodium bicarbonate and sodium chloride in a ratio of X:Y, Y being the concentration of sodium chloride in the dialysis bicarbonate concentrate and Y being at least 28 and less than about 200.

6. A composition comprising sodium bicarbonate and sodium chloride, expressed in gram ratios as follows: $w \text{ NaHCO}_3 : x \text{ NaCl}$ wherein "w" is the desired concentration in grams per liter of sodium bicarbonate in a hemodialysis bicarbonate concentrate prepared from said composition and x is a value of greater than 28.

7. A composition for use in preparing dialysis solution from acid concentrate and a bicarbonate concentrate, said acid concentrate comprising:

- a) sodium chloride;
- b) calcium chloride;
- c) potassium chloride;
- d) magnesium chloride;
- e) acetic acid;
- f) dextrose; and
- g) the concentration of said sodium chloride being less than about 164 grams per liter.

8. A bacteriostatic bicarbonate concentrate composition for use in preparing hemodialysis solution from an acid concentrate and a bicarbonate concentrate, the bacteriostatic bicarbonate concentrate comprising:

- a) sodium chloride;
- b) sodium bicarbonate; and
- c) water, said sodium bicarbonate being at a concentration of between about 50 and about 164 grams per liter, and said sodium chloride being at a concentration of between about 28 and about 200 grams per liter.

9. Combinable aqueous bacteriostatic concentrates for forming upon dilution dialysis solution for using in human dialysis comprising:

a) an acid concentrate including calcium chloride, potassium chloride, magnesium chloride; acetic acid, dextrose and sodium chloride;

b) bicarbonate concentrate including sodium bicarbonate and sodium chloride, said sodium chloride being at a concentration of at least 28 grams per liter, the maximum sodium chloride concentration being about 200 grams per liter.

10. A bacteriostatic bicarbonate concentrate for use in preparing dialysis solution for use in dialyzing animals, said dialysis solution having between about 80 to about 120 milliequivalents each of sodium and chloride derived from sodium bicarbonate, said bicarbonate concentrate comprising:

a) all of the sodium bicarbonate required to yield 15-45 milliequivalents of bicarbonate in the dialysis solution; and

b) sodium chloride in an amount equal to or greater than 28 grams per liter up to all of the sodium and chloride derived from sodium chloride in the dialysis solution.

11. A composition for use in preparing a bacteriostatic bicarbonate concentrate for use in preparing hemodialysis solution, said composition comprising:

a) sodium chloride;

b) sodium bicarbonate; and

c) said sodium chloride being in a quantity such that upon dilution with water to yield a sodium bicarbonate concentration of between about 50 and 164 grams per liter, said sodium chloride concentration will be at least 28 grams per liter and less than about 200 grams per liter.

AMENDED CLAIMS

[received by the International Bureau on 18 March 1986 (18.03.86);
original claims 1, 3, and 4 cancelled; claims 2 and 9 amended; new claim 12 added (3 pages)]

1. (Cancelled)
2. (Amended) In a composition for use in preparing animal dialysis solution from an acid concentrate and a bicarbonate concentrate, said bicarbonate concentrate comprising:
 - a) sodium bicarbonate;
 - b) sodium chloride; and
 - c) water, the improvement comprising: a sodium chloride concentration being at least 28 grams per liter of water and no greater than 200 grams per liter thereby making the concentration bacteriostatic.
3. (Cancelled)
4. (Cancelled)
5. A composition for use in preparing dialysis bicarbonate concentrate, wherein the desired concentration

9. Combinable aqueous bacteriostatic concentrates for forming upon dilution dialysis solution for using in human dialysis comprising:

a) an acid concentrate including calcium chloride, potassium chloride, magnesium chloride; acetic acid, dextrose and sodium chloride;

b) bicarbonate concentrate including sodium bicarbonate and sodium chloride, said sodium chloride being at a concentration of at least 28 grams per liter, the maximum sodium chloride concentration being about 200 grams per liter.

10. A bacteriostatic bicarbonate concentrate for use in preparing dialysis solution for use in dialyzing animals, said dialysis solution having between about 80 to about 120 milliequivalents each of sodium and chloride derived from sodium bicarbonate, said bicarbonate concentrate comprising:

a) all of the sodium bicarbonate required to yield 15-45 milliequivalents of bicarbonate in the dialysis solution; and


b) sodium chloride in an amount equal to or greater than 28 grams per liter up to all of the sodium and chloride derived from sodium chloride in the dialysis solution.

11. A composition for use in preparing a bacteriostatic bicarbonate concentrate for use in preparing hemodialysis solution, said composition comprising:

a) sodium chloride;

b) sodium bicarbonate;

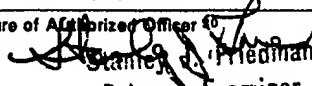
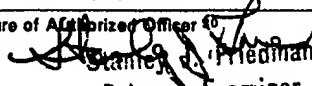
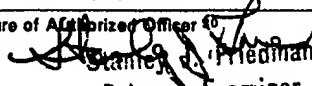
c) said sodium chloride being in a quantity such that upon dilution with water to yield a sodium bicarbonate concentration of between about 50 and 164 grams per liter, said sodium chloride concentration will be at least 28 grams per liter and less than about 200 grams per liter.



12. In a bicarbonat dialysis concentrate comprising water, sodium chloride and sodium bicarbonate, the improvement comprising: a sodium chloride concentration greater than 28 grams per liter and less than the solubility limit of sodium chloride in water, said concentrate thereby being bacteriostatic.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US85/02375

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC INT. CL ⁴ A61K 33/06 - 33/10 - 33/14 and 33/20																	
II. FIELDS SEARCHED <div style="text-align: center; margin-top: 10px;">Minimum Documentation Searched ⁴</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%;">Classification System</th> <th style="width: 75%;">Classification Symbols</th> </tr> <tr> <td style="text-align: center; vertical-align: middle;">US</td> <td style="text-align: center; vertical-align: middle;">424/149, 153, 154 and 156</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵</div>			Classification System	Classification Symbols	US	424/149, 153, 154 and 156											
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<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>¹⁵ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Δ" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search ² <div style="text-align: center; font-size: 1.2em;">17 December 1985</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report ³ <div style="text-align: center; font-size: 1.2em;">24 JAN 1986</div> </td> </tr> <tr> <td style="width: 50%; padding: 5px;"> International Searching Authority ¹ <div style="text-align: center; font-size: 1.2em;">ISA/US</div> </td> <td style="width: 50%; padding: 5px;"> Signature of Authorized Officer ¹⁰ <div style="text-align: center;">  Stanley J. Friedman Primary Examiner </div> </td> </tr> </table>			Date of the Actual Completion of the International Search ² <div style="text-align: center; font-size: 1.2em;">17 December 1985</div>	Date of Mailing of this International Search Report ³ <div style="text-align: center; font-size: 1.2em;">24 JAN 1986</div>	International Searching Authority ¹ <div style="text-align: center; font-size: 1.2em;">ISA/US</div>	Signature of Authorized Officer ¹⁰ <div style="text-align: center;">  Stanley J. Friedman Primary Examiner </div>											
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